Questions for the TC:

1. To assess trends over time in all-cause mortality between 01/01/2006 and latest capture of SIDIAP in people with type 2 diabetes and without diabetes.

2. To assess the differences and ratios in all-cause mortality rates in people with type 2 diabetes and without diabetes between 01/01/2006 and the latest capture of SIDIAP.

Q1:

\* Type 2 diabetes populations:

-Type 2 diabetes incident cases in the study period (2006-2017) or prevalent cases each year?

We understand Incident cases from different generations, to be confirmed.

Comment: that’s correct, people with type 2 diabetes will be followed up from the Diabetes Diagnosis date, till the end of the study or death. If possible, we can also expand the study period (2006-2018).

\*Objective:

- Estimate the mortality ~~incidence~~ between inclusion date (incident date) and end of follow-up (2017) in Diabetes subjects, in different generations (2006-2017)?

And estimate the same in a control group without Diabetes

Comment: those patients who will have diagnose of DM2 recently (i.e. during 2018), will probably have a very short follow-up period.

Comment: that is okay, even short period can contribute to follow-up person-years; to be consistent with UK and Canada, we can include the type 2 diabetes incidence cases by the end of 2018, if possible.

We understand both objectives (1 and 2) are the same. What are the differences between objective 1 and 2? To be confirmed.

Comment:

objective 1: we will investigate the all-cause mortality trends and cardio-renal-metabolic mortality trends for people with and without diabetes, by age and calendar year; stratified by sex (and ethnicity if available);

Objective 2: we will calculate the risk ratio and risk difference between people with and without diabetes, by age and calendar year, stratified by sex (and ethnicity if available);

Yes they are very similar, Objective 2 is based on objective 1, just additional calculation of risk ratio and risk difference.

\*Control group (non-diabetes):

Does the control group need matching (ratio 1:5)? By the year of birth, gender and general practice, and calendar time. Ok (to be confirmed)

Comment: in practice, if you match by year of birth, it is already matched by calendar time. So in short, yes 1:5 match by year of birth (+/-1year), gender and practice, it is possible that some cases cannot find 5 controls, it is okay to keep them, as many as possible and up to 5.

Which methodology we have to use for the sampling of the control group (by risk set or frequency)

A) Perform risk set matching by incidence density sampling

o When a case (DM) is identified we have to looking for 5 controls.

o Control patient can be a future diabetic patient. In this case, their follow-up would be censured.

o Using time (incidence) density sampling. Controls are selected when a case developed the outcome (matching on time)

B) Matching by frequency:

o Exact matching, sub-classification, Nearest Neighbour, Optimal matching, etc by propensity score?

o Potential control group: Any control subject without diabetes during the study period (2006-2007)?

o Problems: Potential Healthy bias( such as immortality bias)

Please choose between 2 methods, and confirm each point by point

Comment:

Match by frequency exact match

This is a descriptive study, we intend not to adjust for many covariates, so we will do exact matching by year of birth (+/- 1year), sex and practice only. Therefore, we don’t need propensity score matching.

Potential control group: any subject without diabetes (T1DM, T2DM or GDM) before the end of study (31/12/2018); met the criteria for age (minimum 34 by the end of study (31/12/2018), maximum 100 years at the beginning of study (01/01/2006))

As we have to exclude patients with prevalent conditions and cancer before the index date (and death before index date for controls), if it is not possible to do it in matching process, I would suggest matching more controls first (e.g. 1:7) and then exclude ineligible patients to keep 5 controls (UK and Canada have done this way). Note: in this way, if the T2DM case was excluded at data cleaning stage, controls matched to this T2DM case shall be excluded as well.

Match without replacement, i.e. one control can be only used once. In final database, we will have distinct patient IDs for cases and controls.

Immortal time bias: we have included all incident T2DM patients, who will contribute to exposed groups’ follow-ups, I don’t think there is immortal time bias.

\*Death line for the delivering of the first report, would it be for October?

Make a teleconference in September after the vacations, please confirm possible dates?

Comment: I hope we can get some initial results in September as we will need to report progress to our funding body, the final report in October is fine.

So far I don’t have any appointment in September except Tuesdays in first and fourth week. As far as I know, Francesco has clinical commitment on Thursday and Friday, so I would avoid these days.

Q6: We will deliver the analyzed data, do you have any template for the tables with variables, and how would you like to receive the data?

Please if you could send us examples of the tables, outcomes, etc.

Comment: I have prepared flowchart and table1, R codes for analysis and outcome outputs will be available soon.